

REMARKS

Upon entry of the present amendment, claims 6 to 11 and 15 to 24 will be pending. Claims 1 to 5 and 12 to 14 have been canceled without prejudice or disclaimer. Claims 6 to 11 stand withdrawn by the Office. New claims 15 to 24 have been added. Support for the new claims can be found throughout the originally filed specification and claims. Specifically, support for claim 15 can be found at, *e.g.*, page 2, line 23, to page 3, line 2; page 3, line 8; page 4, lines 14 to 22; page 8, lines 7 to 21; and page 28, lines 18 to 30, of the substitute specification filed June 9, 2006. Claims 16 to 18 are supported at, *e.g.*, page 8, lines 20 and 21; and page 8, line 36, to page 9, line 22. Claim 19 finds support at, *e.g.*, page 2, lines 21 to 24; and page 9, line 2. Claim 20 is supported at, *e.g.*, page 1, line 20. Claims 21 and 22 are supported at, *e.g.*, page 3, lines 11 and 12; and page 4, line 30. Claim 23 finds support at, *e.g.*, page 3, lines 13 and 14; and original claim 12. Claim 24 is supported at, *e.g.*, page 4, lines 14 to 22; page 8, lines 2 to 17; page 9, lines 23 to 28; and page 18, lines 24 to 27. No new matter has been added.

Information Disclosure Statements

Applicants acknowledge the Examiner's statement that the references cited in 14 Information Disclosure Statements (IDSs) have been considered. Applicants note for the record that a 15th IDS, filed on January 15, 2010, was also considered. Regarding the IDS filed August 5, 2009, the Office signed, but did not date, page 4 of Form PTO-1449. Applicants request that the Examiner send a signed and dated copy of page 4 of the Form PTO-1449. Further, reference 188 on page 10 of that same IDS was lined through and not considered because no date was provided with the reference. Applicants re-submit a complete citation of that reference with the Form PTO-1449 being filed with this Amendment and request that the Examiner consider all the references listed in that form and return an initialed copy of the Form PTO-1449 with the next Office Communication.

Applicants also note that reference 5 of the Information Disclosure Statement filed on January 20, 2009, citing Tawara *et al.* (U.S. Patent No. 7,262,278), was not marked as having

been considered. Applicants respectfully request that this reference be considered and initialed by the Examiner.

Objection to Abstract

The Office objected to the abstract because it contains more than one paragraph. *See*, the Office action at page 2. The abstract has been amended above to be in the form of a single paragraph. A clean copy of the abstract is also provided as Attachment A. Applicants submit that this amendment obviates the present objection and request that it be withdrawn.

Obviousness-Type Double Patenting Rejection

Claims 1 to 4 and 12 to 14 were rejected for nonstatutory, obviousness-type double patenting as being unpatentable over claims 40 to 42, 55, and 59 of U.S. Application No. 10/582,413. *See*, the Office action at pages 3 and 4.

Applicants do not concede that claims 1 to 4 and 12 to 14 are obvious, however, for reasons unrelated to the present rejection, claims 1 to 4 and 12 to 14 have been canceled. Accordingly, the rejection should be withdrawn.

Rejections under 35 U.S.C. § 112, ¶ 2

Claims 1 to 5 and 12 to 14 were rejected for allegedly being indefinite. *See*, the Office action at page 4. Although not acquiescing in the rejection, Applicants have canceled claims 1 to 5 and 12 to 14, obviating the present rejection.

Rejections under 35 U.S.C. § 102(e)

Claims 1 to 5 and 12 to 14 were rejected as purportedly being anticipated by Fukushima *et al.* (US 2004/0242847; "Fukushima"). *See*, the Office action at page 5. As discussed above, Applicants have canceled claims 1 to 5 and 12 to 14, rendering this rejection moot. To the extent that the above grounds for rejection may be applied to new claims 15 to 24, Applicants respectfully traverse.

Independent claim 15 is drawn to methods that require “a plurality of whole antibodies that bind to a given antigen [i.e., all of the antibodies of the plurality bind to the same antigen], wherein the plurality of whole antibodies comprises antibodies with weak or undetectable agonistic activity for the antigen.” In other words, while each of the antibodies binds to the given antigen, they are not all capable of agonizing the antigen to a significant degree. At least some of the antibodies of the plurality must agonize the antigen only weakly, or not at all.

Fukushima describes experiments with three different whole antibodies, two of which (12B5 and 12E10) bind to MPL and another of which (MABL-2) binds to a different antigen, CD47. Of the three disclosed antibodies, the only “plurality of whole antibodies that bind to a given antigen” (as required by claim 15) is the “plurality” made up of 12B5 and 12E10, both of which bind MPL. Fukushima discloses that one (and only one) of those two whole antibodies has weak or undetectable agonistic activity for MPL. (*See*, Fukushima at ¶ [0369] and Fig. 58, which show that the whole antibody 12E10 IgG has undetectable agonistic activity for MPL; and at ¶ [0325] and Fig. 51, which show that the other whole antibody, 12B5 IgG, has strong agonistic activity for MPL.) Since Fukushima’s “plurality” of two anti-MPL antibodies includes only one antibody with weak or undetectable agonistic activity for the antigen, it does not meet the claim 15 requirement “wherein the plurality of whole antibodies comprises antibodies [i.e., more than one antibody] with weak or undetectable agonistic activity for the antigen.” Fukushima discloses no other plurality of whole antibodies that bind to a given antigen. Thus, claim 15 is novel over the prior art.

Claims 16 to 24 depend from claim 15 and therefore are also novel for at least the same reasons. Applicants note that several dependent claims include other limitations that further distinguish over Fukushima.

For example, the list of antigens in claim 18 does not include MPL (a thrombopoietin receptor), the antigen to which Fukushima’s antibodies 12B5 and 12E10 bind, or CD47 (referred to in Fukushima as “Integrin Associated Protein,” or IAP), the antigen to which Fukushima’s MABL-2 binds. While Fukushima does provide a list of other receptors at ¶ [0044], no antibodies binding to any of those receptors and having what could be characterized as “weak or

undetectable agonistic activity for the antigen” are disclosed. Thus, claim 18 further distinguishes over Fukushima.

Claim 23 specifies that the agonistic activities of the whole antibodies are not assayed prior to the step of producing a minibody of each whole antibody. While the Office action at page 5 says that “Fukushima teaches the agonist activity is not determined before the antibody is modified” and points to Fukushima at Example 6 and ¶¶ [0324] and [0325] for support, Applicants find nothing at those locations in Fukushima, nor anywhere else in the reference, to support this assertion, and ask the Examiner for clarification. Fukushima discusses side-by-side assays that are performed on each whole antibody and its minibody forms, so necessarily after the minibodies have been made. Insofar as Applicants can ascertain, the reference is silent on the question of whether any of the whole antibodies was also tested for its agonist activity prior to producing minibody versions of the whole antibody. Silence on this question is not a “teaching” one way or the other about whether the agonist activity was determined before the minibodies were made. Nor can one assume that claim 23’s limitation is “inherent” in Fukushima’s methods, as it is equally plausible that the agonist activity was indeed previously determined by Fukushima (or someone else), and simply not reported in Fukushima. Under U.S. law, inherent anticipation requires that any claim limitation not explicitly found in the reference have been necessarily inherently present in the method disclosed in the reference. A mere possibility is not sufficient.

Claim 24 requires that the plurality of whole antibodies be together in a mixture. In contrast, Fukushima describes handling antibodies separately (*see*, Examples 6, 7, and 8 for MABL-2, 12B5, and 12E10, respectively). Thus, claim 24 further distinguishes over Fukushima’s methods.

Applicants submit that Fukushima does not anticipate the presently claimed methods and ask that the rejection be withdrawn and the claims allowed.

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The fee for the Petition for Three-Month Extension of Time (\$1110) is being paid on the electronic filing system by way of deposit account authorization. Apply any other charges or credits to Deposit Account No. 06-1050, referencing Attorney Docket No. 14875-0163US1.

Respectfully submitted,

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